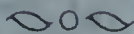


NOTE ON  
THE CONSTITUTION OF  
 *$\alpha$* -ELATERIN

BY

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CXCIII.—*Note on the Constitution of  $\alpha$ -Elaterin.*

By CHARLES WATSON MOORE.

UNDER the title of "elaterin," the British and United States Pharmacopœias recognise a crystalline principle obtained from elaterium—a sediment from the juice of the fruit of *Ecballium Elaterium*, A. Richard.

It has been shown by Power and Moore (*Pharm. J.*, 1909, [iv], 29, 501) that elaterin consists of a mixture of two crystalline



substances of apparently identical percentage composition, but having optical rotations of opposite sign, and which those authors have designated as  $\alpha$ - and  $\beta$ -elaterin (Trans., 1909, **95**, 1985). Of these two substances, only the dextrorotatory,  $\beta$ -elaterin, possesses physiological activity, the lævorotatory,  $\alpha$ -elaterin, which is the principal constituent of the elaterin of commerce, being quite inert.

Berg (*Bull. Soc. chim.*, 1897, [iii], **17**, 85) has stated that elaterin does not exist as such in the fruit of *Ecballium Elaterium*, but that it is formed, after the expression of the juice, by the action of an enzyme on an amorphous glucoside. This view is not in agreement with the results obtained by Power and Moore (Trans., 1909, **95**, 1985), it having been definitely established by those authors that no glucoside of elaterin was present in the fruit of *Ecballium Elaterium*. Recently, Berg (*Bull. Soc. chim.*, 1910, [iv], **7**, 385), in support of his earlier view, has described the characters of the so-called "glucoside" of elaterin, and recorded an analysis of it. This "glucoside" is, however, an amorphous, indefinite product, evidently consisting of a mixture of substances, and any deductions made from the analysis of such material with respect to its composition have little or no value. The present author therefore, with the concurrence of Dr. F. B. Power, sees no reason to depart from the view previously expressed (*loc. cit.*), that elaterin is not present in the form of a glucoside in the fruit of *Ecballium Elaterium*.

It has quite recently been shown by Power and Moore (this vol., p. 99) that  $\alpha$ -elaterin likewise occurs in the fruit of *Citrullus Colocynthis*, Schrader, and the material employed in the present investigation was obtained from this source.

During the last few years elaterin has been the subject of a considerable number of investigations, and, while the presence of certain groups in the molecule has been established, there is still divergence of opinion among the different investigators as to the empirical formula of the substance.

The formula adopted for elaterin by the Pharmacopœias, namely,  $C_{20}H_{28}O_5$ , is that put forward by Zwenger (*Annalen*, 1842, **43**, 460), but more recently Berg (*Bull. Soc. chim.*, 1905, [iii], **35**, 435), Hemmelmayr (*Ber.*, 1906, **39**, 3652), and Thoms (*Apoth. Zeit.*, 1906, **21**, 803) have suggested different empirical formulæ, namely,  $C_{28}H_{38}O_7$ ,  $C_{24}H_{34}O_6$ , and  $C_{22}H_{30}O_6$  respectively.

Of these formulæ, that indicated by Thoms (*loc. cit.*) is not in agreement with the analytical results obtained by all other investigators, while those of Zwenger, Berg, and Hemmelmayr require almost identical percentages of carbon and hydrogen, as follows:

$C_{20}H_{28}O_5$ (Zwenger)	requires	$C=68.9$ ; $H=8.0$	per cent.
$C_{28}H_{38}O_7$ (Berg)	„	$C=69.1$ ; $H=7.8$	„
$C_{24}H_{34}O_6$ (Hemmelmayr)	„	$C=68.9$ ; $H=8.0$	„
$C_{22}H_{30}O_6$ (Thoms)	„	$C=67.7$ ; $H=7.7$	„

Owing to the slight solubility of elaterin in most solvents, molecular-weight determinations of this substance by means of the cryoscopic or the ebullioscopic methods are not trustworthy, and different results have been obtained by various investigators. Thus, Pollak (*Ber.*, 1906, **39**, 3380) obtained results in agreement with Berg's formula by means of the cryoscopic method, using phenol as solvent, whilst by the employment of the ebullioscopic method, using ethylene bromide as solvent, he obtained figures more in agreement with the formulæ of Zwenger and Thoms. Power and Moore (*Pharm. J.*, 1909, [iv], **29**, 501), on the other hand, have obtained results in agreement with the formula of Berg by means of the ebullioscopic method, using chloroform as solvent.

It is necessary, therefore, to have recourse to chemical methods to establish the molecular weight of this substance, but as all the hitherto described derivatives and decomposition products of elaterin are indefinite and amorphous, no satisfactory conclusions can be arrived at regarding their empirical formulæ.

It has been shown by Berg (*Bull. Soc. chim.*, 1905, [iii], **35**, 435) that when elaterin is treated for a short time with alcoholic sodium hydroxide, one molecule of acetic acid is split off, an amorphous, phenolic substance, "elateridin," being formed. Elaterin therefore appears to contain an acetyl group, and the estimation of the acetic acid formed by its hydrolysis affords evidence in support of Berg's formula.

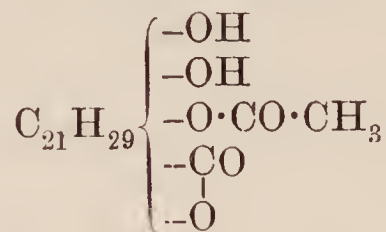
Elaterin appears also to contain a lactone grouping, as by the prolonged action of boiling sodium hydroxide solution it is converted into "elateric acid," which, like "elateridin," is an amorphous product (Berg, *Bull. Soc. chim.*, 1905, [iii], **35**, 435; *Compt. rend.*, 1909, **148**, 1679). Thoms (*loc. cit.*) assumes the presence of two lactone groupings in elaterin, whilst Hemmelmayr (*loc. cit.*) explains the formation of "elateric acid" as being due to the oxidation of an aldehyde group. The latter explanation, however, does not appear to be tenable, for, although Hemmelmayr (*loc. cit.*) describes the preparation of a dihydrazone of elaterin (see also Berg, *Compt. rend.*, 1906, **143**, 1161), the present author has been unable to obtain any evidence as to the presence of a carbonyl group. The "hydrazone" described by Hemmelmayr is an amorphous, indefinite product, and there is no evidence that it is not a phenylhydrazide. Moreover, as such a compound would be obtained by the action of phenylhydrazine on a lactone grouping,



this appears to be the most likely explanation of the nature of the product.

On heating elaterin with acetic anhydride, a diacetyl derivative is formed (Berg, *Bull. Soc. chim.*, 1905, [iii], **35**, 435; Hemmelmayr, *Ber.*, 1906, **39**, 3653). Elaterin must therefore contain two hydroxyl groups.

If it be assumed that the empirical formula put forward by Hemmelmayr is correct,  $\alpha$ -elaterin might be written as follows:

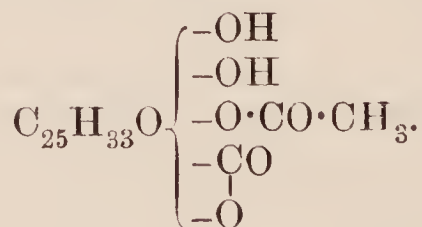


On the other hand, if the empirical formula of Berg be adopted, there remains the state of combination of one oxygen atom to account for.

The present author has now been able to show that by the oxidation of "elateric acid" a definite, crystalline diketone is formed, which possesses the empirical formula,  $\text{C}_{24}\text{H}_{30}\text{O}_5$ , and may be designated *elaterone*.

As "elateric acid" is an indefinite, amorphous product, views as to its constitution, or even its empirical formula, based on analysis are of little or no value. It may, however, safely be assumed that it contains at least two carbon atoms less than elaterin, owing to the removal of the acetyl group from that substance in the course of its formation. As elaterone has now been shown to contain twenty-four carbon atoms, it follows that elaterin must contain at least twenty-six, and accordingly, to bring its formula into harmony with the analytical results, this must be written as  $\text{C}_{28}\text{H}_{38}\text{O}_7$ , in agreement with the formula of Berg.

In the present state of our knowledge, therefore, the formula of  $\alpha$ -elaterin may be written as shown below, the manner of combination of one of the seven oxygen atoms being unknown:



It is probable that the oxygen atom above referred to is present in the form of an ether linking, although, as has been shown by Pollak (*Ber.*, 1906, **39**, 3880), no methoxyl or ethoxyl group is present.

It has been shown by Thoms (*loc. cit.*) that elaterin is very probably a derivative of naphthalene, since by oxidising elaterin,

and distilling the product with zinc dust, he obtained  $\alpha$ -methylnaphthalene. The present author, however, by the distillation of elaterin itself with zinc dust, has obtained 1:4-dimethylnaphthalene.

#### EXPERIMENTAL.

The  $\alpha$ -elaterin employed in the present investigation was obtained from Turkish colocynth, consisting of the dried, peeled fruit of *Citrullus Colocynthis*, Schrader, as described by Power and Moore (this vol., p. 99).

As already stated by those authors (*loc. cit.*),  $\alpha$ -elaterin forms colourless, hexagonal prisms, melting and decomposing at  $232^{\circ}$ , and has  $[\alpha]_D -68.9^{\circ}$  in chloroform solution (compare Berg, *Compt. rend.*, 1910, **150**, 981). On analysis, it gave results agreeing with those found by most other investigators for elaterin. (Found, C=68.9; H=8.1.)

A determination of the iodine value, by Hübl's method, gave the following result:

0.5010 absorbed 0.2673 iodine. Iodine value=53.3.

$C_{28}H_{38}O_7$ , containing one double linking, requires iodine value=52.2.

$\alpha$ -Elaterin is insoluble in cold aqueous sodium or potassium hydroxide, but if it is suspended in a small quantity of alcohol, and potassium hydroxide (1 molecule) added to this mixture, the  $\alpha$ -elaterin rapidly dissolves, and is not precipitated on pouring the alcoholic solution into twice its volume of water. On acidification, however, unchanged  $\alpha$ -elaterin is precipitated. Hence it appears that  $\alpha$ -elaterin possesses phenolic properties, and is capable of forming a potassium derivative soluble in alcohol. Attempts to isolate this potassium derivative were, however, unsuccessful, for on keeping the alcoholic solution, even in the cold, hydrolysis occurred with the formation of "elateridin." Attempts to prepare the corresponding methyl derivative by means of sodium ethoxide and methyl iodide were also unsuccessful.

With consideration of the statements of Berg and Hemmelmayr that elaterin contains a carbonyl group (*loc. cit.*), attempts were made to prepare a hydrazone and an oxime. An alcoholic solution of  $\alpha$ -elaterin was boiled for about one hour with phenylhydrazine (1 molecule), but only resinous products resulted. Two experiments were accordingly made at the ordinary temperature. In both cases 1 gram of  $\alpha$ -elaterin was dissolved in 100 c.c. of alcohol, and in one experiment 0.25 gram of phenylhydrazine was added to the solution, whilst in the second experiment, 0.5 gram of phenylhydrazine was used. The solutions were kept at the ordinary temperature for some hours, and were then diluted with water, when in both cases quantities of a yellow, resinous precipitate were



produced. These precipitates were collected, and attempts were made to crystallise them from various solvents. In both cases small quantities of unchanged  $\alpha$ -elaterin were recovered, but there was no indication of the formation of a definite hydrazone. Similar results were obtained on attempting to prepare an oxime. On boiling the alcoholic solution of  $\alpha$ -elaterin with hydroxylamine, there was some decomposition, but when the experiment was conducted at the ordinary temperature (kept twenty-four hours), over 80 per cent. of the  $\alpha$ -elaterin was recovered unchanged.

A quantity (10 grams) of  $\alpha$ -elaterin was distilled, in small quantities at a time, with zinc dust in a current of hydrogen, when a small amount of an oily liquid, possessing a strong naphthalene-like odour, was formed. This was purified by distillation in a current of steam, but as the quantity of volatile substance so obtained was very small, it was converted into its picrate for identification. This crystallised from alcohol in small, orange-coloured needles, melting at  $139^{\circ}$ , and agreed in all respects with the picrate of 1:4-dimethylnaphthalene.

#### *Alkaline Hydrolysis of $\alpha$ -Elaterin.*

It has been shown by Berg (*loc. cit.*) that elaterin is hydrolysed by alkali hydroxides with formation of one molecule of acetic acid and either "elateridin" or "elateric acid," according to the extent of the hydrolysis. A determination of the acetic acid formed in this reaction was made as follows:

Twenty grams of  $\alpha$ -elaterin were boiled for five hours with an excess of aqueous sodium hydroxide. The alkaline solution was then acidified with sulphuric acid, and the volatile acids removed by a current of steam. The acid distillate was found to consist of a mixture of acetic and formic acids.

The total volatile acids neutralised 1.791 grams NaOH, and the amount of formic acid was found to be equivalent to 0.151 gram NaOH. Hence the acetic acid was 2.460 grams = 12.3 per cent.:

$\text{C}_{26}\text{H}_{35}\text{O}_5 \cdot \text{O}(\text{CO} \cdot \text{CH}_3)$  requires acetic acid = 12.3 per cent.

#### *Oxidation of "Elateric Acid."*

##### (1) *Formation of Elaterone, $\text{C}_{24}\text{H}_{30}\text{O}_5$ .*

The "elateric acid" was prepared by the action of potassium hydroxide on  $\alpha$ -elaterin, according to the method already described by Berg (*loc. cit.*). It forms a light brown, amorphous powder, soluble in sodium hydrogen carbonate, and appears to contain a carboxyl group. Neither the acid, nor any of its salts, has been obtained in a crystalline state. A determination of its specific rotatory power gave the following result:



0.3200, made up to 20 c.c. with ethyl acetate, gave  $\alpha_D + 46'$  in a 2-dcm. tube, whence  $[\alpha]_D + 23.9^\circ$ .

Ten grams of "elateric acid" were dissolved in 100 grams of glacial acetic acid, and 10 grams of chromic acid, dissolved in 12 grams of water, added, after which the solution was heated on a water-bath. A vigorous reaction occurred, and the liquid boiled spontaneously for some minutes. The mixture was subsequently heated for one hour, then poured into water, and, after the addition of sulphuric acid, it was extracted with chloroform. The chloroform extracts were shaken with aqueous sodium carbonate, which, however, only removed small quantities of resinous material. The chloroform solution was accordingly dried, and the solvent removed, when a quantity of a crystalline substance was obtained. This was recrystallised from boiling alcohol, when it formed long, colourless needles, melting at about  $300^\circ$ . The quantity so obtained amounted to 1.4 grams:

0.1135 gave 0.3000  $\text{CO}_2$  and 0.0805  $\text{H}_2\text{O}$ .  $\text{C} = 72.1$ ;  $\text{H} = 7.9$ .

After recrystallising from alcohol it was again analysed:

0.1390 gave 0.3680  $\text{CO}_2$  and 0.0974  $\text{H}_2\text{O}$ .  $\text{C} = 72.2$ ;  $\text{H} = 7.8$ .

$\text{C}_{24}\text{H}_{30}\text{O}_5$  requires  $\text{C} = 72.4$ ;  $\text{H} = 7.5$  per cent.

The molecular weight of the substance was determined by the cryoscopic method in benzene solution:

0.2616, in 22.34 c.c. benzene, gave  $\Delta t = -0.154^\circ$ .  $\text{M.W.} = 380$ .

$\text{C}_{24}\text{H}_{30}\text{O}_5$  requires  $\text{M.W.} = 398$ .

As this substance does not agree in its properties with any compound of this formula which has hitherto been described, it is proposed to designate it *elaterone*, with consideration of the fact that it is a ketone (see below).

Elaterone is sparingly soluble in ether and alcohol, but readily so in chloroform and benzene. On heating, it sublimes in microscopic needles. It contains no hydroxyl group, being unaffected by prolonged boiling with acetic anhydride, and is not changed by boiling alcoholic potassium hydroxide. A determination of its specific rotatory power gave the following result:

0.2185, made up to 20 c.c. with chloroform, gave  $\alpha_D + 2^\circ 38'$  in a 2-dcm. tube, whence  $[\alpha]_D + 120.5^\circ$ .

*Elateronemonophenylhydrazone*.—Elaterone and phenylhydrazine readily interact in acetic acid solution, but if the mixture be heated, only resinous products result. When, however, the reaction is carried out in the cold, and only allowed to proceed for about fifteen minutes, a *monophenylhydrazone* is formed. This crystallises from dilute acetic acid in golden-yellow plates, melting and decomposing at  $278^\circ$ :

0.0988 gave 5.8 c.c. N at  $24^{\circ}$  and 746 mm.  $N=6.4$ .

$C_{30}H_{36}O_4N_2$  requires  $N=5.7$  per cent.

*Elateronedioxime*.—Elaterone was boiled for some hours with an alcoholic solution of hydroxylamine. On concentrating the mixture, a dioxime separated in small, colourless plates, melting and decomposing at  $295^{\circ}$ :

0.2086 gave 11.0 c.c. N at  $18^{\circ}$  and 764 mm.  $N=6.2$ .

$C_{24}H_{32}O_5N_2$  requires  $N=6.5$  per cent.

It is therefore evident that elaterone contains two carbonyl groups, both of which appear to be ketonic, as on boiling it with chromic acid solution, it is much more slowly oxidised than would be the case with an aldehyde.

A quantity (1.5 grams) of elaterone was boiled for one hour with chromic acid (1.5 grams: 6 atoms of oxygen) in acetic acid solution. At the end of this time, however, 0.5 gram of elaterone was recovered unchanged. No definite oxidation products of elaterone have as yet been obtained.

## (2) *Formation of a Compound, $C_{24}H_{32}O_4$ .*

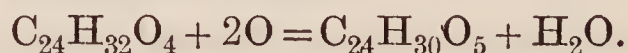
If "elateric acid" be subjected to a somewhat milder oxidation than that described in connexion with the formation of elaterone, two crystalline products are formed, in about equal amounts.

A quantity (2.5 grams) of "elateric acid" was dissolved in glacial acetic acid (25 grams), and to the solution chromic acid (1.6 grams) dissolved in water (3 grams) was added. The solution was heated on a water-bath for one hour, and then worked up as in the previously described oxidation. In this case, however, a crystalline product was obtained, melting at  $225-235^{\circ}$ , which, after fractional crystallisation from alcohol, was separated into two substances, one of which melted at  $295-300^{\circ}$ , and was evidently elaterone, while the other formed glistening plates, melting at  $230^{\circ}$ . The quantity of the second substance was only 0.2 gram. Like elaterone, it was neutral towards alkalis, and did not react with acetic anhydride, but the quantity of material available was too small for full investigation:

0.1175 gave 0.3224  $CO_2$  and 0.0895  $H_2O$ .  $C=74.8$ ;  $H=8.5$ .

$C_{24}H_{32}O_4$  requires  $C=75.0$ ;  $H=8.3$  per cent.

It thus appears probable that this *substance* is an intermediate compound in the formation of elaterone, and that it yields the latter according to the following equation:



With the object of continuing this investigation, an attempt was made to obtain a further quantity of  $\alpha$ -elaterin from a good specimen



of commercial colocynth pulp, but only a very small quantity of the desired compound could be isolated. This result is somewhat remarkable, as Power and Moore (*loc. cit.*) had previously obtained over 1 per cent. of  $\alpha$ -elaterin from Turkish colocynth pulp. It is therefore evident that the amount of  $\alpha$ -elaterin contained in colocynth pulp may vary very greatly.

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